Cell

Blood Scent

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http://dx.doi.org/10.1016/j.cell.2013.11.006

Blood cell production is tightly regulated by cell-intrinsic mechanisms and environmental factors. The study by Utpal Banerjee and colleagues and colleagues reveals that, in *Drosophila*, olfactory signals control hematopoietic progenitor maintenance, thus uncovering a physiological link between sensory perception and hematopoietic response to environmental stress.

The hematopoietic microenvironment, or "niche," can be viewed as a complex network of molecular signals and biomechanical forces that is responsible for non-cell-autonomous control of progenitor and stem cell fate decisions (Frenette et al., 2013). As postulated by Schofield, its main physiological purpose is to regulate self-renewal, quiescence, and differentiation of immature cells, thereby ensuring preservation of the stem cell pool (Schofield, 1978). Studies over the last decade revealed several molecules contributing to extrinsic control of hematopoiesis, such as CXCL12, kit ligand, and VCAM-1, which are locally generated and operate at the HSPC-niche interface. Yet, hematopoietic cells represent fundamental aspects of host defense that must also respond to challenges to the organism, suggesting that systemic factors also participate in regulating stem cells. One example is interferon-γ in mice that, when released during chronic infection, modifies stem and progenitor cell proliferation (Baldridge et al., 2010). Other signals from a distance also play a role, as photic cues governing CNS circadian oscillations can directly affect primitive hematopoietic cells, modifying their localization in the bone marrow (Méndez-Ferrer et al., 2009). Defining how physiologic context modulates stem cells is critical to understanding how tissue or organismal state is translated into activity at the root of a dynamic tissue like blood.

Shim et al. had previously used the sophisticated tools offered by the *Drosophila* model to demonstrate that hematopoietic progenitors are able to sense systemic hormonal (insulin) and nutritional (essential amino acids) signals (Shim et al., 2012). In the current study, they evaluated signals that are external to the organism to determine whether they could be perceived and converted into modulation of hematopoiesis (Shim et al., 2013). With elegant and comprehensive studies, the authors made a further significant advance by demonstrating a functional link between olfactory input and differentiation fate of myeloid progenitors. They describe a novel regulatory pathway, which is activated upon olfactory stimulation of the odorant receptor Or24a. The signals are then transmitted to the brain via olfactory receptor neurons and stimulate secretion of the neurotransmitter γ-aminobutyric acid (GABA) by Kurs6$^+$GABA$^+$ neurosecretory cells. GABA is subsequently released into systemic circulation and binds to the metabotropic $GABA_B$ receptor on hematopoietic progenitors. This in turn increases the concentration of cytosolic calcium and inhibits hematopoietic differentiation. Importantly, the authors show that this pathway is separate from the one mentioned earlier, which controls hematopoiesis via nutritional signals. Although the specific odorous molecule sensed by Or42a has not been defined, the authors showed that it is likely contained within low molecular weight compounds present in the odors from normal food. Notably, larvae raised on minimal odor environments were unable to maintain a pool of normal hematopoietic progenitors as they were lost through differentiation. This crucial observation was confirmed by disruption of the newly identified pathway (Figure 1) at several points using genetic tools.

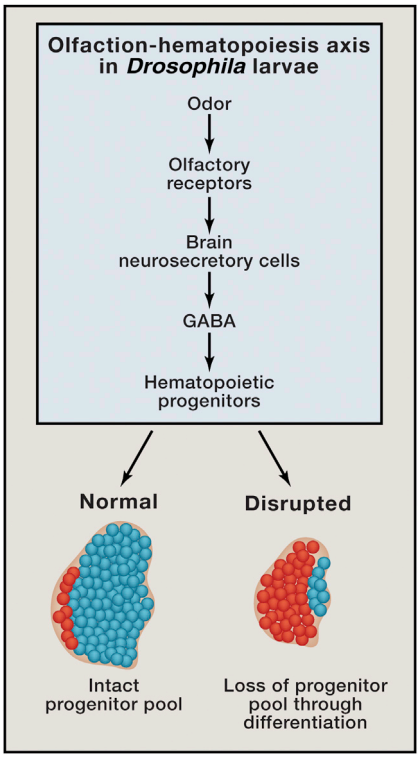

Figure 1. Regulation of Hematopoiesis by Olfaction in *Drosophila* Larvae
Activation of olfactory receptors in *Drosophila* larvae leads to a systemic release of GABA, regulating the proliferation of blood progenitor cells in the lymph gland.

Even though the study is limited to the larval stage of *Drosophila* development and olfaction as a single mode of sensory perception, it raises a tantalizing question of whether a link between a sensory input (perhaps involving a different mode of

perception) and hematopoiesis also exists in higher organisms. If this was the case, the study suggests that, by modulating sensory input, it might be possible to influence hematopoietic regeneration. In a perhaps extreme example, patients with leukemia undergoing hematopoietic stem cell transplantation experience severe, protracted pain due to mucosal damage during pretransplant conditioning and suffer from an altered sense of smell and taste (Epstein et al., 2002). Whether this abnormal sensory input (which in the case of pain is also mediated by GABA, among other molecules) has any effect on the kinetics of posttransplant hematopoietic progenitor regeneration is currently unknown, but the study by Shim et al. hints that such events may result in more than just uncomfortable symptoms. Human HSPCs do express the $GABA_B$ receptor, making the sensorium-hematopoiesis link humans at least a theoretical possibility (Steidl et al., 2004).

The study also makes a valuable addition to the growing body of evidence supporting a key role of systemic signals in progenitor maintenance. Tissues and the cells that comprise, maintain, and repair them are not islands unto themselves. They are indeed "a part of the main" (Donne, 1623), and Shin et al. have begun to teach us just how the main communicates external input into action at the progenitor level.

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